Original Article

Monitoring Response to Osteoporosis Therapy with Alendronate by a Multisite Ultrasound Device

A Prospective Study

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Abstract

Background: Osteoporotic fractures are a major health problem among postmenopausal women. A significant proportion of subjects with low bone density are currently undiagnosed. Peripheral devices can be used for osteoporosis diagnosis, but their role in long-term monitoring of skeletal changes is unclear. The current study evaluated the ability of quantitative ultrasound (QUS) measurements to follow osteoporotic subjects treated with alendronate.

Methods: QUS measurements were done with Sunlight Omnisense™ (Omnisense, Sunlight Medical Ltd., Tel Aviv, Israel), which determines the bone speed of sound (SOS) in several skeletal sites. Postmenopausal women with T-scores of – 2 or less at one site were recruited and treated with alendronate for at least 1 yr. Follow-up was done with QUS and dual-energy X-ray absorptiometry (DXA) (Lunar DPX scanner, Madison, WI, USA) measurements.

Results: After 12 mo, bone mineral density (BMD) increased significantly at the lumbar spine (LS) (0.34 ± 0.08 T-score, $p = 0.0001$ with 95% CI [0.19, 0.49]) and QUS at the tibia (TIB) (0.21 ± 0.09 T-score, $p = 0.02$ with 95% CI [0.03, 0.39]). After 12 mo, a significant increase in mean T-scores was demonstrated in all sites assessed according to baseline T-score of –2 or less.

Conclusions: Peripheral QUS measurement may be considered for follow-up on skeletal changes in response to alendronate treatment.

Key Words: Osteoporosis; quantitative ultrasound; alendronate; bone density; monitoring treatment; multi-site.

Introduction

Osteoporosis is a prevalent disorder, distributed worldwide, affecting mainly postmenopausal women and the elderly population. Treatment of this condition aims at prevention of the characteristic fractures that are associated with significant morbidity and an increased mortality. Osteoporosis therapeutic options include hormone replacement therapy (HRT), calcitonin, estrogen receptor modulators, and bisphosphonates. During treatment, the reduced risk for osteoporotic fractures is coupled with a halt in further bone mineral density (BMD) decline and often with an increase in BMD *(1–4)*.

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Alendronate (Fosamax, MSD) is a potent bisphosphonate that has proven efficacy *(1,2,5,6)* in treating postmenopausal osteoporosis. Alendronate administration increases BMD both at the hip and vertebral column as compared with placebo *(1,6),* leading to a significant decrease in osteoporotic fractures *(1,2,5).*

BMD as assessed by dual-energy X-ray absorptiometry (DXA) is the most studied and employed method for the diagnosis and monitoring of therapeutic response in osteoporosis. However, access to DXA measurements is still limited, leading to underdiagnosis of osteoporosis, especially in the elderly population *(8).* Furthermore, monitoring osteoporotic treatment with DXA measurements in these patients is even more problematic owing to their difficulty in receiving access to these devices, generally located in secondary care facilities. Quantitative ultrasound (QUS)-based techniques were introduced in recent years for a similar purpose. Their advantages over DXA are their easy portability, lower cost, and lack of radiation *(7).* Whereas the role of QUS devices in the diagnosis of osteoporosis and fracture-risk assessment is well-established *(8–10),* there are only a few conflicting reports on QUS monitoring of skeletal response to treatment *(11–17).* Sunlight Omnisense™ (Omnisense) is a QUS device that measures the speed of sound (SOS) along the bone, at different skeletal sites. Using Omnisense facilitates applying diagnostic World Health Organization (WHO) criteria for osteoporosis in the general population *(19)* and discriminates between patients with and without fragility fractures *(20,21).* The combination of multiple skeletal-site SOS measurements may have a better diagnostic yield than the single-site determination *(22).* As a result of its high precision and multisite capability, Omnisense may have a role in monitoring bone changes over time resulting from aging, disease, or treatment. To evaluate this option, we conducted a longitudinal study of postmenopausal women treated with alendronate. Follow-up on skeletal changes was performed with Omnisense and with DXA measurements. This report describes the results from the first year of the follow-up.

Materials and Methods

Patients

Consecutive Caucasian postmenopausal women evaluated for osteoporosis were recruited for this study. Women were enrolled in the study after assignment to alendronate treatment by the treating physician. Subjects underwent a baseline QUS assessment and answered a detailed questionnaire. Women were eligible if they had an SOS result equal to or less than –2 SD compared to peak SOS (T-score) at least at one of the accessible measured sites *(23)* and were willing to comply with the 2-yr follow-up. Candidates were excluded from the study if they used a medication known to affect bone metabolism in the 12 mo prior to the study. Other exclusion criteria were current hyperthyroidism; primary hyperparathyroidism; other chronic diseases known to affect bone metabolism such as malabsorption syndrome, lactose intolerance, chronic liver or renal disease, Paget's disease, or cancer (other than skin cancer) within the last 10 years; and eating disorders.

Study Design

All women started receiving 10 mg of alendronate daily upon enrollment, and were scheduled for follow-up visits every 6 mo for 2 yr (a total of five visits). During each visit, drug compliance was assessed and SOS was measured. Bone density was assessed by DXA at baseline and annually thereafter (a total of three visits).

QUS Measurements

Measurements were performed using the Sunlight Omnisense™ (Omnisense, Sunlight Medical Ltd., Tel Aviv, Israel) as previously described *(19–21).* Omnisense determines bone SOS of an ultrasound wave with a frequency of 1.25 MHz as it propagates axially along cortical bone. Three skeletal sites were measured, each with its own unique probe, including the distal 1/3 radius (RAD), the proximal phalanx of the third finger (PLX), and the mid shaft tibia (TIB). Measurements were carried out on patient's nondominant limb *(19,21,22).* Precision of SOS measurements with the Omnisense at the radius, tibia, and phalanx were 0.44, 0.59, and 0.44%, respectively *(21,24).*

Bone Density Measurements

BMD was measured at the lumbar (L2–L4) spine (LS) and femoral neck (FN) by DXA (Lunar DPX scanner, Madison, WI, USA).

Ethics Considerations

The local and national ethics committees approved the study protocol, and all participants signed an informed consent form.

Statistical Analysis

DXA and QUS data were expressed in T-scores. Data was analyzed by SPSS software version 11. T-test compared the mean change in each site over time. The percent of patients with positive change from baseline was also calculated for each site. We used the calculation of the Trend Assessment Margin (TAM) calculated as $1.8 \times$ short-term precision (%) to assess the significance of positive changes in QUS and BMD measurements. Since a response to Alendronate treatment was expected and was demonstrated in previous studies, we used this less stringent criteria. Changes exceeding $1.8 \times$ short-term precision (%) were considered significant with a confidence interval of 80% *(25)*.

To evaluate the difference in bone changes between the two techniques, we compared the average of the change from baseline divided by the standard deviation (SD) of each technique.

Results

A total of 68 women were enrolled in the study. Baseline characteristics of the participants are shown in Table 1. The lowest BMD and SOS were measured at the LS and RAD, respectively. Mean patient age and body mass index (BMI) in subgroups of those with T-score <–2 in single sites did not differ from that of the entire cohort of women (data not shown). Number of subjects with a baseline T-score of –2 or less at the LS, FN, TIB, RAD, and PLX were 45, 32, 22, 32, and 48, respectively.

Whereas BMD at the FN remained stable during the 12 mo of treatment, a significant increase in BMD T-score at the LS was demonstrated (0.34 ± 0.08, $p = 0.0001$ with 95% CI [0.19, 0.49]). A positive change was noted in 80% of the participants (Table 2). At the TIB, a significant increase in SOS was noted after 12 mo (0.21 ± 0.09, $p = 0.02$ with 95% CI [0.03, 0.39]) with a positive change in 71% of the participants. To compare degree of changes at the LS to those noticed at the TIB, the average of the change from baseline divided by the SD of each technique was calculated.

Table 1
Baseline Patient Characteristics

	Site	Mean ± SD
Age (yr)		67.2 ± 8.5
BMI (kg/m^2)		25.9 ± 4.3
BMD (T-score)	LS	–3.03 ± 1.03
	FN	–2.02 ± 0.99
SOS (T-score)	RAD	–2.62 ± 1.18
	PLX	–2.5 ± 1.04
	TIB	–1.77 ± 1.1

Table 2
Bone Response to Treatment at 12 Mo

	Site (n)	T-score change (mean ± SE)	Subjects with positive bone response (%)
BMD	LS (41)	0.34 ± 0.08* [0.19, 0.49]**	80
	FN (41)	–0.04 ± 0.10 [–0.25, 0.17]	51
SOS	RAD (32)	0.05 ± 0.10 [–0.16, 0.25]	50
	PLX (38)	0.01 ± 0.10 [–0.19, 0.21]	47
	TIB (36)	0.21 ± 0.09† [0.03, 0.39]	71

* $p = 0.0001$, **95% Confidence Interval, †$p = 0.02$

A positive change of 36.6 and 20% was noted at the LS and TIB, respectively (degree of change was not significantly different between the two techniques). Mean FN BMD and SOS at the RAD and PLX of the entire study group did not change throughout the first 12 mo of treatment.

Subanalysis of patients with T-scores of –2 or less at baseline in each specific site revealed a significant increase from baseline in all SOS and BMD measurement sites following 12 mo of treatment (Table 3). A positive change from baseline of 35.8, 24.3, 14.2, and 12.8% was noted at the LS, TIB, RAD, and PLX, respectively (again no significant difference was found when comparing degree of change between LS, TIB, and RAD). In 71–86% of partici-

Table 3
Bone Response to Treatment at 12 Mo in Subjects
with a T-Score –2 or Less

	Site (n)	T-score change (mean ± SE)	Subjects with positive bone response (%)
BMD	LS (36)	0.42 ± 0.06* [0.30, 0.54]**	86
	FN (22)	0.13 ± 0.05† [0.02, 0.24]	59
SOS	RAD (21)	0.25 ± 0.11† [0.008, 0.49]	71
	PLX (28)	0.19 ± 0.08† [0.025, 0.35]	54
	TIB (14)	0.25 ± 0.09† [0.06, 0.43]	86

* $p < 0.001$, **95% Confidence Interval, †$p < 0.05$

pants, a positive change was found at the LS, RAD, and TIB, as opposed to 54–59% at the FN and PLX. BMD changes were significant in 75 and 31.8% of patients assessed at the LS and FN, respectively, whereas SOS changes were significant in 43% of patients assessed at the TIB and the RAD.

Discussion

Osteoporosis is a major health problem with an estimated treatment cost of $13.8 billion per year for treating osteoporotic fractures in the US alone *(26)*. In a large epidemiological study, it was recently demonstrated that almost half of previously undiagnosed postmenopausal women had low BMD diagnosed by peripheral devices while 7.2% had osteoporosis *(8)*. The authors of that study concluded that owing to the large proportion of women at risk and the relatively low availability of DXA equipment, there should be a shift of osteoporosis diagnosis and management to the means of evaluation most readily available at primary care. For this purpose, QUS devices appear to be the most suitable. They are small, devoid of radiation exposure, and cheaper than radiation-based devices. Theoretically, QUS devices assess "bone mass," however, other parameters such as bone elasticity and micro-architecture influence the results *(7)*. In addition, elderly patients frequently have spinal osteophytes that lead to spuri-

ously high spinal BMD *(7)*. QUS measurement is not prone to this osteoarthritis interference.

Monitoring skeletal response to osteoporosis treatment is important for identifying patients who fail to respond to treatment and to facilitate patient compliance with therapy. Whereas DXA is the most frequently used tool for these purposes, the role of QUS is less well-established. Several longitudinal studies were conducted with conflicting results. Using different QUS devices, some reported improvement by bone sonographic parameters induced by various anti-resorption agents *(11–15,17)*, whereas others were able to determine bone response only by DXA and not QUS *(16)*. A recent prospective study evaluated the ability of heel ultrasonography to monitor osteoporotic patients treated with alendronate. In this study, it was demonstrated that QUS at the heel, and in particular stiffness parameter, seems to be a sensitive tool for monitoring the response to alendronate *(18)*.

The main finding of this study is increased SOS at the TIB in postmenopausal women treated with alendronate for 12 mo. SOS increased at the tibia after 6 mo and increased further after 12 mo in a similar manner to lumbar spine measurements. Furthermore, when only patients with a T-score of –2.0 SD or less at baseline in each site were included in the analysis, T-scores improved significantly in all sites and a significant change was noted in 75 and 31.8% of subjects at the LS and FN, respectively, and in 43% of subjects at the TIB and RAD. To evaluate the degree of change in bone parameters owing to treatment between two methods using different parameters (i.e., BMD in mg/cm^2 and SOS in m/s), a common basis for comparison must be used. In this study we compared the average of the change from baseline divided by the SD of each method. No significant difference in the degree of bone changes was found between LS and RAD or TIB.

Our data of the alendronate-induced SOS increase measured by Omnisense are in accordance with a previous report *(15)*. However, they diverge from the results of another study that used a once-weekly alendronate dosing *(27)*. One limitation of that study is that all participants were treated with selective estrogen receptor modulator until 6 mo prior to enrollment, whereas the patients in the current study were newly diagnosed and untreated. In accordance, a previous study comparing women started on anti-resorptive

therapy with women already on therapy and women with no previous therapy revealed that all QUS parameters increased in the first group more than in the group of already treated patients *(17)*. Another major limitation in the conflicting study *(27)* is the inclusion in that study of patients according to baseline BMD T-score. Indeed, some of the baseline QUS-assessed T-scores were not in the osteoporotic range (i.e., baseline tibia T-score –1.3). It was shown that patients with osteoporosis sustain less clinical fractures while on long-term treatment with alendronate, whereas no such benefit was demonstrated for osteopenic women (T-score <–1 to –2.4). *(6)*. Accordingly, one may wonder whether skeletal sites with only mild bone loss demonstrate less increase in bone mass during treatment than sites with a marked loss at baseline. Our study group was chosen according to T-scores assessed by QUS, and indeed we demonstrated that women with T-scores of –2 or less had an increase in T-scores from baseline. A cutoff point of –2 was chosen, based on the fact that treatment is usually recommended for patients with T-scores of –2 and lower. *(23)*.

The response to alendronate therapy measured by QUS varied between the different skeletal sites. Changes at the TIB and RAD were more prominent than at the PLX. Results can be partially explained by the different composition of trabecular and cortical elements in each bone, the influence of alendronate, and the sensitivity of QUS to each of these bone elements.

The main limitations of the current study are the small number of patients enrolled and a lack of BMD measurement following 6 mo of treatment. We feel that not including a placebo-treated group is in accordance with ethical considerations.

We conclude that Omnisense might have a role in monitoring patients' response to treatment with alendronate. It may represent a particularly suitable monitoring tool in the elderly, because it is devoid of the interference of spinal degenerative changes and is readily accessible at the primary care setting. Clearly, additional studies including more patients, additional treatment modalities, and perhaps longer follow-up periods are needed.

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